IN RE APPLICATION OF: Crooke et al.
SERIAL NO: 09/918,026
Response to Office Action Dated: Nov. 18, 2004

REMARKS

Claims 1, 4-10, and 12-13 are pending in the instant patent application. Applicants have herewith presented amendments to claim 1, support for which can be found throughout the specification and claims as originally filed. No new matter has been added.

Rejection under 35 U.S.C. §112, 2nd Paragraph

Claim 1 has been rejected under 35 U.S.C. §112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants respectfully traverse, however, in the interest of advancing prosecution, claim 1 has been amended to replace "compound" with "antisense oligonucleotide." Applicants submit that the rejection is no longer proper and respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. §112, 1st Paragraph

Claim 1 has been rejected under 35 U.S.C. §112, 1st paragraph, as failing to comply with the written description requirement.

Applicants respectfully traverse, however in the interest of advancing prosecution, claim 1 is amended herewith to read "**the** coding region" per the Examiner's suggestion. Applicants submit that the rejection is no longer proper and respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. §102

Claims 1 and 12 have been rejected under 35 U.S.C. §102 (e) as allegedly being anticipated by Cases et al., U.S. Patent No. 6,579,974 ("Cases").

Applicants respectfully traverse. The primer sequence described in Cases (SEQ ID NO: 8) does not meet each and every element of claim 1 as presently amended. Applicants herewith submit a declaration by Mark J. Graham pursuant 37 C.F.R. §1.132 (the "Declaration") demonstrating that the primer of SEQ ID NO: 8 appearing in Cases does not inhibit ACAT-2 expression by at least 60%. *See* Declaration page 3, number 8. Cases (SEQ

ID NO: 8) does not include each and every element of claim 1, because it does not meet this functional element. Applicants submit that the alleged anticipation is improper and respectfully request that the rejection be withdrawn.

Claims 1, 4-10, 12, and 13 have been rejected under 35 U.S.C. §102 (e) as allegedly being anticipated by Cowsert et al., U.S. Patent No. 6,482,644 ("Cowsert").

Applicants respectfully traverse. The antisense oligonucleotide targeting Dual specific phosphatase 8 described in Cowsert (SEQ ID NO: 17) does not meet each and every element of claim 1 as presently amended. Applicants submit that the Declaration demonstrates the antisense compound targeting Dual specific phosphatase 8 (SEQ ID NO: 17) appearing in Cowsert does not inhibit ACAT-2 expression by at least 60%. Cowsert (SEQ ID NO: 17) does not include each and every element of claim 1, therefore, Applicants submit that the alleged anticipation is improper and respectfully request that it be withdrawn.

Claims 1, 4-10, 12, and 13 have been rejected under 35 U.S.C. §102 (b) as allegedly being anticipated by Dean et al., U.S. Patent No. 6,180,353 ("Dean").

Applicants respectfully traverse. The antisense oligonucleotide targeting human daxx described in Dean (SEQ ID NO: 109) does not meet each and every element of claim 1 as presently amended. Applicants submit that the Declaration demonstrates the antisense oligonucleotide targeting human daxx (SEQ ID NO: 109) appearing in Dean does not inhibit ACAT-2 expression by at least 60%. Dean (SEQ ID NO: 109) does not include each and every element of claim 1, therefore Applicants submit that the alleged anticipation is improper and respectfully request that it be withdrawn.

Claims 1, 4-10, 12, and 13 have been rejected under 35 U.S.C. §102 (e) as allegedly being anticipated by Zhang et al., U.S. Patent No. 6,503,754 ("Zhang").

Applicants respectfully traverse. The antisense oligonucleotide targeting human BH3 interacting domain death agonist described in Zhang (SEQ ID NO: 22) does not meet each and every element of claim 1 as presently amended. Applicants submit that the Declaration

demonstrates the antisense oligonucleotide targeting human BH3 interacting domain death agonist (SEQ ID NO: 22) appearing in Zhang does not inhibit ACAT-2 expression by at least 60%. Zhang (SEQ ID NO: 22) does not include each and every element of claim 1, therefore Applicants submit that the alleged anticipation is improper and respectfully request that it be withdrawn.

Rejection under 35 U.S.C. § 103 (a)

Claims 1, 4-10, 12, and 13 have been allegedly rejected under 35 U.S.C. §103 (a) as allegedly being unpatentable over Oelkers et al. in view of Chong et al., and Bennett et al.

Applicants respectfully traverse. A proper *prima facie* case has not been established by the Examiner because the combination of Oelkers et al., Chong et al., and Bennett et al. does not provide sufficient motivation to combine to arrive upon Applicants' pending claims nor does it provide all of the limitations of Applicants' currently pending claims.

Three basic criteria must be met to establish a *prima facie* case of obviousness: (i) suggestion or motivation, either in the relied-upon references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings of the references; (ii) a reasonable expectation of success; and (iii) the relied-upon references must teach or suggest all of the limitations present in the applicant's claims.

Applicants submit that the combination of Chong et al., Oelkers et al., and Bennett et al. references do not provide sufficient motivation to create an inhibitor which targets human acyl-CoA cholesterol acyltransferase-2 (ACAT-2) mRNA of SEQ ID NO: 3 claimed in the instant patent application.

Chong et al. describes efforts in designing inhibitors targeting ACAT proteins to treat and prevent atherosclerosis, but also states the following caveat: "whether inhibition of ACAT will prevent atherosclerosis is not yet clear" (*See* Chong et al., section 4.4.1, paragraph 1). Chong et al. does not describe inhibitors which target ACAT-2 mRNA of SEQ ID NO: 3.

Oelkers et al. describes the human acyl-CoA cholesterol acyltransferase-1 (ACAT-1) and ACAT-2 isoforms and their respective cDNAs. Oelkers et al. does not elucidate with any

certainty functional distinctions between the two ACAT protein isoforms, nor does it describe the mRNA sequence of ACAT-2 of SEQ ID NO: 3.

Bennett et al. is directed to antisense targeting HER-2, a gene unrelated to ACAT-2.

There is no suggestion or motivation contained in the combination of Chong et al., Oelkers et al. and Bennett et al. because there is no teaching of functional differences between the two ACAT protein isoforms, an advantage of designing an inhibitor of ACAT-2, nor a description of inhibiting ACAT-2 mRNA of SEQ ID NO: 3. The suggestion or motivation to make an antisense inhibitor of ACAT-2 mRNA was first described by the Applicants in the present patent application. Applicants therefore respectfully submit, that in absence of such a suggestion or motivation, the *prima facie* case of obviousness based upon Chong et al, Oelkers et al., and Bennett et al. is improper and should be reconsidered and withdrawn.

Applicants submit that the combination of Chong et al., Oelkers et al., and Bennett et al. references do not teach all of the limitations of Applicants' claimed invention.

Chong et al. describes efforts in designing ACAT protein inhibitors to treat and prevent atherosclerosis. Chong et al. does not describe inhibitors which target ACAT-2 mRNA of SEQ ID NO: 3.

Oelkers et al. describes the identification of ACAT-1 and ACAT-2 proteins and their respective cDNAs. Oelkers et al., however, does not disclose the ACAT-2 mRNA of SEQ ID NO: 3.

Bennett et al. is directed to antisense targeting HER-2, a gene unrelated to ACAT-2.

All of the claim limitations are not taught by the combination of Chong et al., Oelkers et al. nor Bennett et al. because there is no teaching of an inhibitor targeting ACAT-2 mRNA of SEQ ID NO: 3, only a teaching of inhibitors targeting ACAT proteins and the existence of the ACAT-2 protein. In fact, Applicants were the first to teach antisense inhibitors which target ACAT-2 mRNA of SEQ ID NO: 3 in the present patent application. Applicants therefore respectfully submit, that in absence of such a teaching, the *prima facie* case of

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obviousness based upon Chong et al, Oelkers et al., and Bennett et al. is improper and should be reconsidered and withdrawn.

Applicants submit that the claims as currently amended are in condition for allowance and respectfully request a timely allowance.

If the Examiner is of a contrary view, the Examiner is requested to contact the undersigned attorney at (760) 603-4631. Please charge any deficiencies to Isis Pharmaceuticals, Inc., Deposit Account No. 50-0252, referencing Attorney Docket No. ISPH-0588.

Respectfully submitted,

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